PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	PUBLICATION OF INTERVENTIONAL PHASE 3 AND 4 CLINICAL TRIALS IN RADIATION ONCOLOGY: AN OBSERVATIONAL STUDY
AUTHORS	Pérez-Alija, Jaime; Gallego, Pedro; Linares, Isabel; Ambroa, Eva; Pedro, Agustí

VERSION 1 - REVIEW

REVIEWER	Cihoric Nikola Department of Radiation Oncology, Inselspital, Bern University Hospital and University of Bern Nikola Cihoric is an owner of a www.clinicaltrial.co, a meta-research portal.
REVIEW RETURNED	11-Feb-2017

GENERAL COMMENTS	This paper describes a rate of publication among finished radiotherapy trials registered on clinical trial registry www.clinicaltrials.gov. The topic of this work is indeed very important and to my best knowledge, it is unique in the field of the radiation therapy. Before publication following points must be addressed: 1) Limitation of search engine Some limitations of a described method must be addressed and discussed. These limitations are before all inherited through: 1 A). An imperfect search of clinicaltrials.gov search engine (searched on 29.01.2017) a. search for term "radiotherapy" returns 9135 trials. b. search for "radiation therapy" returns 9302 trials. c. search for "radiochemotherapy" returns 1339 trials. 1 B). A data entered through protocol registration system are misleading or wrong. For example: a. radiotherapy is not registered within <intervention> field. b. radiotherapeutic interventions are registered in form of the abbreviation (e.g. SBRT, IMRT) c. Intervention classified as <Radiation> is not radiotherapeutic procedure but a diagnostic method, computed tomography or MRI. d. Term Radiation is often used in another context e.g. " NCT00671385 - Survey of Optical Values of the Breast Using Radiation-Free Pressure-Free Optical Scanning" 2) Limitation in www.clinicaltrials.gov database design: A definition of a phase III trials in clinicaltrials.gov. is wrong. For an unknown reason, an administration (designers, whoever) has made a huge mistake and defined phase III trials as follows:

	"For a clinical trial of a drug product (including a biological product), the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21 and in 21 CFR 312.85 for phase 4 studies". "N/A: Trials without phases (for example, studies of devices or behavioral interventions).". This is, of course, clear (!!!!) mistake of a clinicaltrials.gov registry architecture and/or USA administration that governs the registry. It is very likely that a substantial number of trials including or concerning only radiation therapy were registered as trials without phase. Phase III trials, by design, should provide definitive proof that a drug, biological substance, methods, or any interventions are effective with sufficient statistical power on sufficient sample size. 3) Investigators did not evaluate if the radiotherapy was an experimental part of a protocol, standard treatment or optional treatment. We can not be sure if the radiotherapy was in focus of the trial. 4) Investigators have identified 7 trials with "Withdrawn" status. Were there any trials with status Terminated or Suspended? 5) One point should be discussed or at least mentioned: It is known that journals are less likely to publish negative results, especially those with higher impact factor. For a scientist advancement in a career is usually connected with a number of publication in high impact journals. One can ask himself following question: If results of a trials are negative, why give an additional effort to write a manuscript? Can I use this time for something more helpful for my career? Instead, a writing a paper, should I write a grant proposal to receive funding for a new project with a higher likelihood of the positive result and consequent publication? Why is so hard to publish a paper!? It would be certainly interesting to know how many scientists are running their trials besides regular full-time job as clinicians, without protected time for research. 6) Industry-sponsored trials, where radiotherapy is in primary focus, are extremely rare (Cihoric at al. Brachytherapy and Glioblastoma papers, Tsikkinis at al. Prostate Paper). Radiotherapy is mostly used as a standard treatment option or non-obligatory part of a protocol. This should be discussed in the context of a paper. 7) Results submission in clinicaltrials.gov are only compulsory for trials conducted in the USA. A substantial number of trials are conducted out of USA soil. Radiotherapy is a most important tool in the treatment of malignant diseases with substantial influence on patient prognosis and quality of life. Further investigation on a methodology of clinical trials, their lifecycle, and destiny of results and subsequent publications are warranted. A short remark on terminology: Radiooncology vs. Radiation Therapy. Radiation therapy is a method applicable not only for malignant disease but also for numerous benign diseases and disorders. This fact must be acknowledged and discussed. I am aware that in English speaking area radiation therapy is most commonly (or almost always) used for a treatment of malignant disease. However, there are several benign diseases that may be treated efficiently with radiation therapy. According to my personal

	archive (till 2014), approximately 69 trials that evaluate radiation therapy in benign disease were registered. (Analysis of clinical trials in radiation oncology: a systematic characterization of the Clinicaltrials. gov database N Cihoric, A Tsikkinis, DM Aebersold, K Lössl, K Zaugg International Journal of Radiation Oncology, Biology, Physics 1 (90), S581-S582) In short: Major: 1) Limitation and possibility of false negative or false positive results must be declared. Nothing extensive, just in short! Minor: 1) Additional reasons why results are not published! Who is going to publish a negative trial? Why give an effort? Some more discussion... 2) There are few references deserved to be mentioned in context of the manuscript Conclusion: Despite limitations, the manuscript deserves attention. Major limitations must be properly addressed or declared. I will recommend this paper for publication after addressing previously mentioned issues.

REVIEWER	Stephen J Chapman University of Leeds, UK
REVIEW RETURNED	08-Apr-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript, which I enjoyed reading. The authors address the issue of non-publication of phase 3-4 RCTs in radiation oncology and report considerable deficiencies in how the results of these trials are disseminated. The issue of non-publication is not new, however exploring these considerations from the perspective of radiation oncology does add productively to current evidence. I wonder if these results are more appropriate for a speciality journal where they will be better targeted to an expert audience. The authors may wish to consider the following points, which should lead to major revisions of their current manuscript: 1) At present, the aims and results of the study seem unclear. The authors set out to explore non-publication of radiation oncology trials, but focus heavily on the effect of funding (such as NIH and industry). The outcomes should be defined more clearly; if the effect of funding is a major (a priori) outcome, this should be stated in the methods (perhaps as a secondary outcome) 2) The authors currently explore trials registered on ClinicalTrials.gov. It is true that this is probably the largest trial registration database, however, ICMJE mandate registration on any WHO ICTRP database (for which ClinicalTrials.gov is one). The authors may wish to consider trials contained on other databases as they are equally as relevant, or else justify their current selection.

	3) According to the methods, the search on 6th May 2016 identified studies up to 1st Jan 2015. The authors also state that the last identified study was 6th May 2014. Firstly, it would seem odd (but not impossible) that no relevant studies were identified between 6th May 2014 and 1st Jan 2015 - the authors should please clarify. Secondly, the authors should consider if 24 months is long enough for an assessment of publication to be made fully. Otherwise they should justify why 24 months is appropriate. This recent paper may be useful: http://bmjopen.bmj.com/content/7/3/e012212?cpetoc 4) To be absolutely clear, the authors should elaborate on how they selected trials according to their inclusion criteria of "radiotherapy". For instance, did this include all studies in which patients underwent radiotherapy, or only those in which it was the active intervention. 5) In the results, the authors report on "being American" as an outcome variable. This requires clarification according to if it means American nationalism or investigators working from an American institution - quite different. 6) In the results, all references to significance values should be followed by the P value. For instance In the second paragraph of the results (comparison of phase III vs. IV trials), the P value should be stated. 7) In the results (paragraph 5), the authors should justly how or why they chose a value of 16 as the critical value to include trials in their analysis here. 8) There is little discussion on the limitation of this paper. The authors should consider this critically, perhaps using some of the points mentioned herein.

REVIEWER	Sheila Turner National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House, Enterprise Road Southampton SO16 7NS UK
REVIEW RETURNED	11-Apr-2017

GENERAL COMMENTS	1) The paper does not place trials in this clinical area (radiation oncology) in the context of trials in other clinical areas. There is no indication as to whether the findings in this clinical area are in line with other clinical areas or widely different, so is this a widespread problem, or particularly unique to radiation oncology? 2) There may have been other reasons why no results were published and I felt this was not adequately discussed in the paper. I also note that clinicaltrials.gov does have a system where the primary completion date is changed to the actual completion date and I wondered why this date was not used, and how many of the included studies were known to have completed. this was not clear. 3) Not all the acronyms were explained in full. Please put in

	full the first time each is used.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1:

1. Limitations of search engine:
A. We were aware of this problem and we searched taking into account all possible terms related to radiotherapy treatment. We came across more than 10 000 posible trials, but after removing all phase 0, 1 and 2, and taking into account our selection of primary completion dates we finished with a set of a little bit more than 1400 trials. We have to go on this set manually and most of them were false positive findings.
B. Afterwards we had to go manually one by one in order to know if the trial was in fact a radiotherapy trial (radiation therapy only for malignant disease). We couldn't find an automatic way of doing this.
2. We were unaware of this problem, so thank you very much for the information. We perform a new search taking into account all this trials without phase. Since we perform our paper search 6 May 2016 we had to check the "History of Changes" of every trial without phase, in order to discard any modification made after that date. We found 93 new phase 3 or 4 trials we haven't previously account for.
3. We take into account all radiotherapy trials having radiotherapy either as primary focus or standard treatment. We did this because as Radiation Oncologist one has to be aware of all trials conducted having radiotherapy as part of the intervention. For instance, a new drug combined with radiotherapy could boost a side expect or create a new one. This is essential, for example, when discussing cases during tumour board meetings.
4. Yes, there were trials with status Terminated or Suspended. Those trials were taken into account when analysing if trials have reported results in the registry, since it is still compulsory for them to do so. But those trials, as it is said in "Methods ◊ Publication Search in a PRJ", were excluded from our PRJ search, since it makes no sense to try to publish a trial which has not been completed.
5. We totally agreed this might be the case. But from our data we were not able to answer this question, as it is said in the "Discussion" part, because a massive lack of data results in the registry. One way to go would be to e-mail principal investigators and asked them if they had any results from their trials and, if that were the case, if they have found any problems publishing their results (i.e. negative results, changing jobs, research conducted outside their regular job, etc.). We make a point of it by citing "the planning fallacy". When we start a trial we tend to overestimate how good our results are going to be, how easy is going to analysed our data, published them etc.
6. This is an interesting point (how rare are industry-sponsored trials where RT is in primary focus) but we were unaware of that during our work. It will make sense to look into it next time. On the other hand, and we have now clarify this in the "Methods" section, we only take into account radiotherapy either as standard treatment or primary focus.
7. Trials conducted outside the USA but with the intention to apply their results on the USA soil, have to register their trials in the registry and report results of it according to the FDAAA 801. According to the law, results submission is required for applicable clinical trials that were required to be registered under FDAAA 801. We assume most phase 3 or 4 trials conducted in RT would like to apply their results in USA and that was one of the reasons we used this registry. But it is true that, as large as this registry is, many trials conducted in RT are registered in other registries. So our dataset is not the entire population of phase 3 or 4 trials.
We totally agreed further investigation on methodology of clinical trials and how are they reporting their results in the literature is absolutely necessary. But it was out of the scope of this work.

REVIEWER 2:

We also thought these results were more appropriate for a specialty journal to better target to an expert audience. We previously presented an earlier summary of our work in the 2016 ESTRO35 Congress held in Turin, and it was one of the only six communications selected by ESTRO (European Society of Therapeutic Radiation and Oncology) for a press release. A large number of participants showed an interest in our result and we thought, being a very sensitive issue, it should pass a peer-reviewed process in order to assess the quality of our work. But when we tried to publish our findings in our specialty journals we came across with editorial rejection because it “is not appropriate for this journal’s readership”. This is the main reason why we turned to BMJ Open.

1. The main aim of this observational study was to know if phase 3 and 4 conducted in Radiotherapy were being published. We were simply astonished to find that almost 50% of them had not published any results at all, and therefore our evidence is nowadays importantly skewed. It was only secondary to us –at least in this work– to find the causes to this lack of data. But we thought maybe running a statistical analysis testing for funding type would be worth a try. This is why we mention this in Methods ◊ Statistical Analysis. But as it is clearly stated in the Background section, our two main objectives in this work were to answer these two questions: “Were the trials conducted in radiation oncology in compliance with the US law and therefore did they make their results publicly available?” “How many of the trials conducted in radiation oncology have published their results in a peer-reviewed journal (PRJ)?” Those, as we said in our paper, are our vital questions to answer.
2. We totally agreed with that. We chose ClinicalTrial.gov registry not only because is the largest and more relevant database, but because we assumed most phase 3 or 4 trials conducted in radiotherapy would like to apply their results on the USA soil. And trials conducted outside the USA, but with an intention to be applicable there, have to register and submit summary results in the ClinicalTrial.gov registry according to the FDAAA 801. But it is true that, as large as this registry is, many trials conducted in RT are registered in other registries. So our dataset is not the entire population of phase 3 or 4 trials.
3. Because our query was conducted on 6 May 2016 and since we allowed a minimum 24 months for publication in a PRJ, 6 May 2014 was considered for this part of the study. But for the Database search we use 1 January 2015 because we needed only to allow for 12 months for publication of the compulsory summary results in the registry (we actually allowed a little bit more than 12 months, 16 months).
We agree we don’t know, on the other hand, if 24 months is long enough for an assessment of publication. This would be something to look carefully into it was somewhat outside the scope of this work. We simply thought that if all results must have been reported after a 12 months, another 12 months was something realistic for publishing a phase 3 or 4 trial in a paper (usually those trials have a strong evidence and are more easily accepted for publication). We would like to notice anyway that 24 months was a minimum, so most trials studied were given a much more time to publish with a median and mean time to have a publication of 60 months (see figure attached as "To the Editor Only"; We uploaded this image only regarding your question). Although the paper cited for the reviewer is very interesting the aim of that work is different from ours, since they are trying to examine the time delay between funding and publication for government-funded trials, while we were looking for time delay between completion date and publication.
4. Totally agreed. We already clarify this in our paper (Methods ◊ Database Search). We take into account all radiotherapy trials having radiotherapy either as primary focus or standard treatment. We did this because as Radiation Oncologist one has to be aware of all trials conducted having radiotherapy as part of the intervention. For instance, a new drug combined with radiotherapy could boost a side expect or create a new one. This is essential, for example, when discussing cases during tumour board meetings.
5. Being American refers to investigators working from an American institution. We have already clarified this in Methods ◊ Statistical Analysis.
6. We totally agreed with this observation. We have already corrected that.
7. This was a tricky point for us. We didn’t know if it would make any sense to report p-values for

groups with just 2 or 3 trials. That was the only reason since applying those statistical tests to such small sample would hardly make any sense. But we have already corrected that and we extended our analysis to every group.
8. We have further discussed some limitations of our study.

REVIEWER 3:

1. It is true that while conducting our work we were not primarily concerned about placing our work into a more global context. In fact we were targeting a special audience, mainly those working in the radiation oncology field. We also thought these results were more appropriate for a specialty journal to better target to an expert audience. We previously presented an earlier summary of our work in the 2016 ESTRO35 Congress held in Turin, and it was one of the only six communications selected by ESTRO (European Society of Therapeutic Radiation and Oncology) for a press release. A large number of participants showed an interest in our result and we thought, being a very sensitive issue, it should pass a peer-reviewed process in order to assess the quality of our work. But when we tried to publish our findings in our specialty journals we came across with editorial rejection because it "is not appropriate for this journal's readership". This is the main reason why we turned to BMJ Open. However we cited and commented in our discussion an important cross-sectional analysis published in BMJ 2013 (ref. 8) dealing with non-publication of large randomized trials. We also cited and commented in relation to our work another BMJ 2014 paper (ref. 9) dealing with non-publication in another domain, surgical clinical trials.
2. We totally agreed with that. It is hard to discuss why this is happening because our observational study was not designed to find the causes of this result. The main aim of this study was to know if phase 3 and 4 conducted in Radiotherapy were being published. We were simply astonished to find that almost 50% of them had not published any results at all, and therefore our evidence is nowadays importantly skewed. It was only secondary to us –at least in this work– to find the causes to this lack of data. But we thought maybe running a statistical analysis testing for funding type would be worth a try. This is why we mention this in Methods ◊ Statistical Analysis. But as it is clearly stated in the Background section, our two main objectives in this work were to answer these two questions: "Were the trials conducted in radiation oncology in compliance with the US law and therefore did they make their results publicly available?" "How many of the trials conducted in radiation oncology have published their results in a peer-reviewed journal (PRJ)?" Those, as we said in our paper, are our vital questions to answer. You are also right about the registry having a system where it is possible to change the primary completion date, but this feature has no impact on our study. If the primary completion date changed we took this new completion date as our PCD. It is important to note that when a change is made in the PCD the new date still appears in the PCD field of the registry.
3. We went through our paper again and found we had missed API (Application programming interface). Since we used it only once in our text we already changed the acronym for the entire explanation. We have also left without explanation USA (United States of America), and GPS (Global Positioning System) as non-explained acronyms. We did this on purpose because we thought they were nowadays broadly used in our language and might require no further explanation. Below there is a list of acronyms extracted from our paper:
• FDAAA 801: Food and Drug Administration Amendments Act of 2007 (Background)
• PCD: Primary Completion Date (Background)
• PRJ: Peer-reviewed journal (Background)
• NCT: identification code in the ClinicalTrials.gov registry (Methods ◊ Database Search)
• URL: uniform resource locator (Methods ◊ Database Search)
• OR: odds ratio (Methods ◊ Statistical Analysis)
• NIH: National Institutes of Health (Results)

VERSION 2 – REVIEW

REVIEWER	Stephen J Chapman

	University of Leeds
REVIEW RETURNED	27-May-2017

GENERAL COMMENTS	Thank you for the opportunity to revisit this work. The authors have made significant improvement following the first round of reviews. Particularly, thank you for your in-depth responses to previous comments. To pick up on just a few of these: 1) Whilst the issue of "American authors" is clarified in the statistics section, use of this phrase throughout the manuscript is ambiguous. Might it be better to re-phrase this to "authors from american institutions" (or similar). Whilst it may seem a minor point, the implicated difference is noticeable! 2) Thank you for your response regarding time from completion to publication. Your justification for this is fair, but is still missing from the discussion. Inherently, this is an important methodological issue and should be raised for the readers' benefit. My remaining comments are minor and may rest at the editor's discretion: 1) Introduction (Para 2): Justification for using the ClinicalTrials.gov database should go in the Methods section, rather than here. 2) Introduction (Para 3): For clarity, consider simplifying the first research question for ease of reading i.e. "were the results of trials conducted in radiation oncology made publicly available". 3) Methods: Consider transferring bulleted lists into boxes and linking with text 4) Tables: By convention, any P value less than 0.001 should be represented P<0.001 5) Figures: A flow chart of eligibility should be included 6) Preparation: The manuscript would benefit from language & grammar review Thank you again for the opportunity to review this interesting manuscript. Best wishes.

REVIEWER	Sheila Turner NIHR Evaluation, Trials and Studies Coordinating Centre UK
REVIEW RETURNED	26-May-2017

GENERAL COMMENTS	The paper deals with a very important issue, and there is a wider literature available on publication or non-publication of trials. It would have been helpful to have set this study within that context, however, it is the choice of the authors not to do that which is their prerogative. The statistical analysis is an important part of this paper – I am not qualified to comment on this aspect.

VERSION 2 – AUTHOR RESPONSE

To Reviewer 3:

We have agreed to mention in our discussion section that this problem of representation is widely spread in other areas. We changed accordingly our references.

To Reviewer 2:

1. We already changed that. We hope no misunderstanding is now available to the reader. It is important for us to clarify this point and we are thankful for this correction.

2. We have now explicitly justified our choice in the Discussion section.
Minor:

1. We agree. It makes much more sense in Methods and we already changed that.

2. We understand your point because our phrasing is quite complex here. But for us it is important to mention the US law because we used the ClinicalTrials.gov registry in our study.

3. Thank you very much for this suggestion. We already did that.

4. Thank you again for this correction. We knew that and it was a mistake we completely missed in our revisions.

5. We included two flow charts, one dealing with our Database search, the other with the PRJ search.

6. Our initial manuscript was edited and reviewed by a native English biomedical editor in order to meet the editorial standards required by leading English language publications.

VERSION 3 – REVIEW

REVIEWER	Stephen J Chapman University of Leeds
REVIEW RETURNED	14-Jul-2017

GENERAL COMMENTS	Thanks once again for inviting my review of this manuscript. The authors have done a sound job of addressing all comments. Notably, the issue of American-affiliated authors is now clear and the tables provide an improved succinctness to the paper's readability. I have no further concerns. Best wishes.